Effect of Oral Administration of Calcium Carbonate, Aluminum Hydroxide Gel and Dihydrotachysterol on Renal Acidosis

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UEDA, H., IKEDA, H., SASAKI, Y. and SHIOJI, R. *Effect of oral Administration of Calcium Carbonate, Aluminum Hydroxide Gel and Dihydrotachysterol on Renal Acidosis.* Tohoku J. exp. Med., 1978, 124 (1), 1-11 — The effects of oral administration of calcium carbonate, aluminum hydroxide gel, dihydrotachysterol (DHT) and sodium bicarbonate on metabolic acidosis and plasma calcium and phosphate were studied in 7 patients with chronic renal failure. Single administration of calcium carbonate alleviated the acidosis and increased the urinary bicarbonate excretion. These effects were potentiated when aluminum hydroxide gel was administered in combination with calcium carbonate. The plasma calcium was increased by this combination therapy. The effects of these two agents on acidosis and plasma calcium were further enhanced by the additional administration of DHT. Urinary bicarbonate excretion was less during the treatment with aluminum hydroxide gel and calcium carbonate than with aluminum hydroxide gel and sodium bicarbonate, when the excretions were compared at the similar concentrations of plasma bicarbonate. Aluminum hydroxide gel and DHT are likely to enhance the effect of calcium carbonate, which works as an alkalinizing salt on acidosis, probably through increasing calcium absorption in the intestine. And the three agents suppress the leak of bicarbonate into the urine contributing to the improvement of acidosis. ——— calcium carbonate; renal acidosis; aluminum hydroxide gel; dihydrotachysterol; bicarbonate excretion

The favorable effect of calcium carbonate on metabolic acidosis in patients with chronic renal failure has been reported (Clarkson et al. 1966; Makoff et al. 1969). But a negative view has also been reported (Berlyne 1971).

In chronic renal failure, the secondary hyperparathyroidism is cited as a factor leading to an increase in the tubular leak of bicarbonate, eventually causing metabolic acidosis (Muldowney et al. 1970). Then it can be suggested that oral administration of calcium carbonate may alleviate acidosis through suppression of parathyroid hormone secretion due to elevation of the plasma calcium. There is also a report noting calcium carbonate as an effective alkalinizing salt on metabolic acidosis in patients with chronic renal failure (Clarkson et al. 1966). Such alkalinizing effect of calcium carbonate is presumed to be correlated with the amounts to be absorbed by the intestine. If the intestinal absorption of calcium

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can be increased by some measures, they will be useful for the treatment of chronic renal acidosis with calcium carbonate.

Aluminum hydroxide gel, administered orally, does not affect the acid-base equilibrium (Hurst et al. 1963), but long-term administration of aluminum hydroxide gel has been reported to augment intestinal absorption of calcium (Lotz et al. 1968; Ansari 1970). Dihydrotachysterol (DHT) increases intestinal absorption of calcium not only in normal persons but also in patients with chronic renal failure (Liu and Chu 1943). In the present study, calcium carbonate, aluminum hydroxide gel and DHT were administered, alone or in combinations, to patients with chronic renal failure to treat their metabolic acidosis, and the effects were analyzed and compared.

MATERIALS AND METHODS

The subjects were 7 patients with chronic renal failure including 2 with idiopathic Fanconi syndrome. Their clinical data are shown in Table 1.

Intake of salt was restricted to 3 g a day in one case (M.W.) and 7 g a day in three cases (S.S., Y.M. and K.T.), while free salt intake was allowed in the remaining three cases (K.S., M.S. and T.S.).

Daily doses of calcium carbonate were from 3 to 8 g, aluminum hydroxide gel from 3 to 6 g, and DHT from 0.25 to 2.0 mg.

In all cases, 24-hr urine was collected in a vessel containing mineral oil and thymol as preservative. The urine samples were stored in a refrigerator. Urinary pH, carbon dioxide content, ammonium, titratable acid (TA), creatinine, sodium, potassium, and phosphate were measured within a few days. As a rule, arterial and venous blood were sampled twice a week before breakfast to determine arterial plasma pH and bicarbonate, and venous plasma sodium, potassium, calcium, phosphate, and creatinine. The arterial plasma pH and bicarbonate were measured by Astrup microequipment at 37°C. Venous plasma concentrations were measured for calcium by OCPC method and for phosphate by Fiske-Subbarows' method, each using the autoanalyzer M 500-Hitachi. Urinary pH was measured by Beckman pH-meter SS-2, carbon dioxide content by Van Slyke manometric apparatus (Van Slyke and Neill 1924), ammonium by Conway's microdiffusion method (Conway 1950), and titratable acid by Henderson-Palmer's method (Henderson and Palmer 1914). The urinary bicarbonate concentration was computed from the values of carbon dioxide content and pH, using $pK' = 6.33 - 0.5\sqrt{(Na^+) + (K^+) + (NH_4^+)}$, according to the Henderson-Hasselbalch's equation.

TABLE 1. *Laboratory data of*

Patient	Age	Sex	Blood urea nitrogen (mg/100 ml)	Creatinine clearance (ml/min/ 1.48 m ² *)		
					pH	P _{CO₂} (mmHg)
1	K.S.	13	M	54	7.3	31.7
2	S.S.	28	F	54	9.7	34.7
3	Y.M.	13	M	64	10.1	30.3
4	M.W.	23	F	41	5.5	35.7
5	K.T.	19	M	90	2.9	24.7
6	M.S.	18	F	98	5.1	27.8
7	T.S.	21	M	88	8.0	24.0

* Body surface area of average Japanese adult. † King-Armstrong units.

RESULTS

Effects of calcium carbonate on metabolic acidosis, and plasma calcium and phosphate (Figs. 1-3).

Of 3 cases (K.S., S.S. and Y.M.) treated with calcium carbonate at a daily dose of 5g, acidosis was alleviated in 2 (K.S. and Y.M.), but remained unchanged in the other one (S.S.). The concentration of plasma calcium did not change in all three, while the concentration of plasma phosphate decreased in 2 (S.S. and Y.M.) and remained unchanged in the other one (K.S.). Urinary bicarbonate excretion was increased in 2 (K.S., and Y.M.) with an alleviation in acidosis, but remained unchanged in the other one (S.S.) without alleviation in acidosis.

Effects of calcium carbonate administered in combination with aluminum hydroxide gel on metabolic acidosis, and plasma calcium and phosphate (Figs. 1-6).

Combined administration of calcium carbonate and aluminum hydroxide gel alleviated the acidosis in 5 (K.S., S.S., Y.M., M.S. and T.S.) of 6 cases, compared with the pretreatment level. In the remaining one (M.W.) in which plasma bicarbonate had not been checked before the combined therapy, the concentration decreased after discontinuation of the combined therapy. Furthermore, in all 4 cases (K.S., S.S., Y.M. and T.S.) to which calcium carbonate was administered alone before the combined therapy, the amelioration was more remarkable during the combined therapy than calcium carbonate alone. The concentration of plasma calcium was increased in 5 (K.S., S.S., Y.M., M.S. and T.S.) of 6 cases, compared with the pretreatment level. In the remaining one (M.W.) in which plasma calcium had not been checked before the combined therapy, the concentration dropped after discontinuation of the combined therapy. Furthermore, in 3 (K.S., S.S. and Y.M.) of 4 cases (K.S., S.S., Y.M. and T.S.) in which calcium carbonate was administered alone before the combined therapy, the increase of plasma calcium was more remarkable during the combined therapy than calcium carbonate alone. The concentration of plasma phosphate, compared with the pretreatment level, was decreased by the combined therapy in 5 (K.S., S.S., Y.M., M.S. and T.S.) of 6 cases.

7 patients with chronic renal failure

Plasma						Remarks
HCO ₃ (mEq/liter)	Ca (mg/100 ml)	P (mg/100 ml)	K (mEq/liter)	Cl (mEq/liter)	Alkali phosphatase (K.A. units†)	
15.2	6.6	6.6	3.4	107	40	Fanconi syndrome
18.1	8.7	6.0	5.0	112	4.5	
14.1	8.7	8.7	4.0	111	27.3	
19.4	7.4	8.4	4.3	107	9.2	
9.0	4.4	8.3	4.2	110	51.0	
15.0	4.4	9.2	4.6	105	15.7	Fanconi syndrome
12.6	6.7	7.1	4.0	108	15.7	

Case 1. K. S.

Fig. 1

Case 2. S. S.

Fig. 2

Fig. 1. Case 1. Effects of calcium carbonate, aluminum hydroxide gel, sodium bicarbonate and dihydrotachysterol on plasma concentrations of bicarbonate, calcium and phosphate and on urinary excretion of bicarbonate. nd, not determined.

Fig. 2. Case 2. Effects of calcium carbonate, aluminum hydroxide gel and sodium bicarbonate on plasma concentrations of bicarbonate, calcium and phosphate and on urinary excretion of bicarbonate.

In the remaining one (M.W.) in which pretreatment concentration of plasma phosphate had not been checked, its level rapidly increased after discontinuation of the combined therapy. In all 4 cases (K.S., S.S., Y.M. and T.S.), the concentration of plasma phosphate was more distinctly decreased during the combined therapy than calcium carbonate alone. Urinary bicarbonate excretion was increased by the combined therapy above the pretreatment level in 5 (K.S., S.S., Y.Y., M.S. and T.S.) of 6 cases. In the remaining one (M.W.) in which urinary bicarbonate had not been checked before the combined therapy, the level decreased after discontinuation of the combined therapy. Urinary bicarbonate excretion was increased to a larger extent during the combined therapy than calcium carbonate alone in 3 (K.S., S.S. and Y.M.) of 4 cases (K.S., S.S., Y.M. and T.S.) to which calcium carbonate was administered alone before the combined therapy. But in patient T.S., urinary bicarbonate excretion, when compared at the similar concentrations of plasma bicarbonate, was considerably less during the administration of

Case 3. Y.M.

Fig. 3

Case 4. M. W.

Fig. 4

Fig. 3. Case 3. Effects of calcium carbonate, aluminum hydroxide gel and sodium bicarbonate on plasma concentrations of bicarbonate, calcium and phosphate and on urinary excretion of bicarbonate.

Fig. 4. Case 4. Effects of calcium carbonate, aluminum hydroxide gel and dihydrota-chysterol on plasma concentrations of bicarbonate, calcium and phosphate and on urinary excretions of bicarbonate and net acid.

aluminum hydroxide gel and calcium carbonate than aluminum hydroxide gel and sodium bicarbonate (Fig. 7). Urinary net acid excretion ($\text{NH}_4^+ + \text{TA} - \text{HCO}_3^-$) determined in 2 cases (M.S. and M.W.) was decreased in one (M.S.) compared with the pretreatment level, while in the other case M.W., in which the pretreatment level had not been checked, the level was increased after discontinuation of the combined therapy.

Effects of simultaneous administration of three agents, calcium carbonate, aluminum hydroxide gel, and DHT on metabolic acidosis, and plasma calcium and phosphate (Figs. 5 and 8).

Calcium carbonate, aluminum hydroxide gel, and DHT were administered simultaneously in 2 cases (M.S. and T.S.). The addition of DHT to calcium carbonate and aluminum hydroxide gel caused a further improvement in acidosis and plasma concentration of calcium, both of which had already been ameliorated

Fig. 5. Case 5. Effects of calcium carbonate, aluminum hydroxide gel and dihydrota-chysterol on plasma concentrations of bicarbonate, calcium and phosphate and on urinary excretions of bicarbonate and net acid.

by administration of the latter two agents. Patient T.S. temporally developed hypercalcemia. The addition of DHT also decreased the concentration of plasma phosphate below the level attained by the administration of calcium carbonate and aluminum hydroxide gel. Urinary bicarbonate excretion was increased after the additional administration of DHT to calcium carbonate and aluminum hydroxide gel in the 2 cases, along with an alleviation in acidosis.

Effects of DHT alone and DHT and aluminum hydroxide gel on metabolic acidosis, and plasma calcium and phosphate (Figs. 1, 4 and 8).

During single administration of DHT in 3 cases (K.S., M.W. and K.T.), the acidosis was ameliorated in one (K.S.), unchanged in one (M.W.), and aggravated in the remaining one (K.T.). DHT and aluminum hydroxide gel were administered to 2 patients who had not responded to DHT alone. During this combination therapy the acidosis was ameliorated in one (M.W.), but not in the other (K.T.). The concentration of plasma calcium increased with DHT alone in only one (K.S.) who showed an alleviation in acidosis, but remained unchanged in the other 2 (M.W. and K.T.) who showed no alleviation in acidosis. In these 2 refractory cases, plasma calcium increased during the combined administration of DHT and

Case 6. T. S.

Fig. 6. Case 6. Effects of calcium carbonate, aluminum hydroxide gel, sodium bicarbonate and dihydrotachysterol on plasma concentrations of bicarbonate, calcium and phosphate, together on urinary excretion of bicarbonate.

Fig. 7. Case 6. Relationship between plasma concentration of bicarbonate and urinary excretion of bicarbonate. Urinary bicarbonate excretion, when compared at the similar concentrations of plasma bicarbonate, was considerably less during the administration of aluminum hydroxide gel and calcium carbonate (o) than aluminum hydroxide gel and sodium bicarbonate. (●).

Case 7. K.T.

Fig. 8. Case 7. Effects of aluminum hydroxide gel and dihydrotachysterol on plasma concentrations of bicarbonate, calcium and phosphate and on urinary excretions of bicarbonate and net acid.

aluminum hydroxide gel. The concentration of plasma phosphate remained unchanged during the administration of DHT alone in 2 (K.S., M.W.) of 3 cases, but increased in the remaining one (K.T.). Plasma phosphate decreased during the combined therapy in 2 cases (M.W. and K.T.). Urinary bicarbonate excretion did not change during the administration of either DHT alone or its combination with aluminum hydroxide gel, irrespective of acidosis ameliorated or not.

DISCUSSION

Orally taken calcium carbonate reacts with gastric hydrochloric acid and is converted to calcium chloride (Hurst et al. 1963) as follows: $\text{CaCO}_3 + 2\text{HCl} \rightarrow \text{CaCl}_2 + \text{H}_2\text{O} + \text{CO}_2$. The production of one molecule of calcium chloride takes up two hydrogen ions. In the intestine, calcium carbonate is absorbed in only minimum amount, but calcium chloride is absorbed relatively easily. Unabsorbed calcium chloride reacts with sodium bicarbonate in the small intestine and converts back to calcium carbonate to be excreted in feces. Therefore, the amount of calcium chloride, produced in the stomach and absorbed in the intestine, accurately accounts for net acid neutralization. In order for calcium carbonate to be effective as an alkalinizing salt, it is indispensable that hydrochloric acid is present in gastric

juice (Ivanovich et al. 1967) and calcium is absorbed by the intestine. This suggests that the effect of calcium carbonate on acidosis may be individually different. In 2 of our 3 cases treated with calcium carbonate alone, acidosis was ameliorated with an increase in urinary bicarbonate excretion. This suggests that calcium carbonate works as an alkalinizing salt.

Long-term administration of aluminum hydroxide gel has been reported to augment intestinal absorption of calcium (Lotz et al. 1968; Ansari 1970). This suggests that the effects of calcium carbonate as an alkalinizing salt would be strengthened by the simultaneous administration of aluminum hydroxide gel. In fact, in all 4 cases, the effect of calcium carbonate alone on acidosis turned more favorable when it was administered in combination with aluminum hydroxide gel.

DHT is said to increase the intestinal absorption of calcium (Liu and Chu 1943). Therefore, DHT can be thought to augment the effects of calcium carbonate as an alkalinizing salt. The additional administration of DHT in combination with calcium carbonate and aluminum hydroxide gel resulted in a marked elevation of plasma bicarbonate and calcium which had already been heightened by calcium carbonate and aluminum hydroxide gel in 2 cases.

Parathyroid hormone is known to increase the urinary bicarbonate excretion, aggravating the renal acidosis already present in patients with chronic renal failure. The elevated plasma calcium concentration after a long-term medication of vitamin D₂ or acute infusion of calcium gluconate is noted to ameliorate the acidosis of chronic renal failure through the elevation of renal bicarbonate threshold (Muldowney et al. 1970).

It has been reported that oral administration of aluminum hydroxide gel elevates the concentration of plasma calcium in patients with chronic renal failure (Clarkson et al. 1972). When compared with the administration of calcium carbonate alone, the concentration of plasma calcium was increased with an alleviation in acidosis in 3 of 4 cases by the combined use of calcium carbonate and aluminum hydroxide gel. This may indicate that aluminum hydroxide gel would promote the effect of calcium carbonate on secondary hyperparathyroidism. In patient T.S., the urinary bicarbonate excretion, when compared at the similar concentrations of plasma bicarbonate, was less when aluminum hydroxide gel and calcium carbonate were given than when aluminum hydroxide gel and sodium bicarbonate were given (Fig. 7). Such a difference in urinary bicarbonate excretion may mean the increase of renal bicarbonate threshold due to the combined use of aluminum hydroxide gel and calcium carbonate, the decrease of renal bicarbonate threshold due to the increase of extracellular fluid volume produced by sodium bicarbonate (Slatopolsky et al. 1970), or the combination of the causes described above.

Of our 3 cases (K.S., M.W. and K.T.) to whom DHT was administered alone, the acidosis was ameliorated in only one (K.S.) in which plasma calcium was elevated. Of 2 cases (M.W. and K.T.) administered DHT in combination with aluminum hydroxide gel, the acidosis was ameliorated in one (M.W.) in which plasma calcium was elevated. However, in view of the fact that the two cases,

in which acidosis was alleviated by the administration of DHT alone or in combination with aluminum hydroxide gel, originally had an insignificant leak of renal bicarbonate excretion and showed no decrease in renal bicarbonate excretion during the administration of DHT, it seems unreasonable to assess the alleviation of the acidosis only by the decrease of renal bicarbonate excretion. Mechanism of the effect of DHT on acidosis remains unknown.

It has been reported that bone mineral is an important buffer reservoir in the defence against metabolic acidosis (Lemann et al. 1966). As another effect of calcium carbonate on acidosis, therefore, it may be cited that increase in intestinal absorption of calcium restores buffer capacity of bone mineral. But we failed to find any definite clue to it.

In patient T.S., the concentration of plasma creatinine rapidly rose with the development of hypercalcemia, suggesting its aggravating effect on renal function. On the other hand, in patient M.S. whose plasma calcium was always normal, there was no appreciable exacerbation in renal function in the course of 14 months of combination therapy by the three agents.

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